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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,604	06/29/2001	Robert A. Hallowitz	BIOT1-11	6514

7590 06/25/2004

Theranostech, Inc.
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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,604	HALLOWITZ ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 14 November, 2003, wherein claims 1, 4, and 8 were amended. Claims 1-16 are currently under examination.

35 U.S.C. § 112, Second Paragraph

Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

The reference to "assessing the infectivity status of a host infected with HIV" is confusing. It is not readily manifest if the claims are simply directed toward the **detection** of HIV in a patient sample (i.e., A method for detecting HIV infection in a patient comprising ...) or if they encompass a method for **predicting disease progression** or **treatment responsiveness** (i.e., A method for predicting disease progression in a patient infected with HIV comprising ...). The disclosure fails to provide sufficient illumination concerning this confusion. For instance, on page 2 of the specification it clearly states that "The phrase "**infectivity status**" is intended as a description of the condition of a host with respect to the HIV virus, e.g., how many cells are actually **infected** with the HIV virus in comparison to the total number of cells which are capable of being infected." Thus, this passage appears to suggest that the crux of the invention is the detection of HIV infection. However, in the same paragraph, the

specification states that "A gp120/CD4 positive cell ratio in accordance with the present invention provides a superior value for assessing **patient treatment** and **HIV disease progression.**" Thus, this passage also appears to be suggesting that the crux of the invention is actually directed toward assessing patient responsiveness to antiviral therapy and the progression to disease. Applicants need to clearly and unambiguously identify the purpose of the invention (i.e., detection of HIV, assessment of treatment responsiveness, assessment of disease progression) and provide sufficient supporting steps that enable the claimed methodology to perform the desired task.

Furthermore, the claims are also incomplete for omitting essential positive methods steps, such omission amounting to a gap between the steps (refer to M.P.E.P. § 2173.05(q)). *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986). The recited method only discloses two incomplete steps, (a) and (b). Step (a) simply involves the measurement of cell-surface gp120 while step (b) simply involves the measurement of $CD4^+$ cells. However, there is no description of a sample preparative step (i.e., are the samples obtained from blood, lymphatic tissues, or some other compartment; are purified populations of cells prepared; etc.). There is no description of suitable controls that validate the claimed methodology. There is no description of a determinative of prognostic procedure wherein some meaningful nexus is established between the test result and purpose of the invention. Appropriate correction is required.

Moreover, the claims still fail to set forth a number of salient characteristics that are required to practice the claimed methodology. For instance, as previously noted the claimed invention is directed toward a method of assessing the "infectivity status" of an HIV-infected host by measuring cell surface gp120 and the number of $CD4^+$ lymphocytes. However, the method is confusing since the preamble clearly states that the subject is **already** HIV-infected. How is the "infectivity status" of the host being

determined if they are already HIV-infected to begin with? Moreover, the claimed methodology simply measures the number of gp120-expressing cells which does not include all those cells infected with HIV since it fails to take into consideration latently infected cells and non- $CD4^+$-infected cells (e.g., B-cells, dendritic cells, $CD8^+$ cells). Applicants should clearly and unambiguously set forth the purpose of the methodology, as supported by the disclosure (i.e., A method for detecting HIV-1 infection in patients undergoing antiviral treatment who are negative by viral co-culture methodologies comprising the following ...), and provide appropriate supporting steps. The claims have also been amended to recite that these measurements are made independently of each other which is confusing. Does the method utilize two independent aliquots from the same sample or two independent samples from the same patient of interest? What type of gp120-expressing cells are measured (i.e., $CD4^+$ cell target, $CD4^-$ cell target, lymphocyte, monocyte, dendritic cells, glial cells, etc.)? What cellular compartment are these cells/samples derived from (i.e., hematopoietic, lymphoreticular, neurological)? Does the methodology require any prescreening or presorting of the biological sample? Moreover, after making these measurements, how are they utilized to ascertain the infectivity status of host already infected with the virus? The salient characteristics of the methodology need to be clearly set forth.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph,

as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward a method of determining the "infectivity status" of a host who is already infected with HIV by measuring the number of cells expressing cell-surface gp120 and the number of $CD4^+$ lymphocytes. As set forth in the preceding paragraphs, it is not readily manifest what the term "infectivity status" encompasses. For the purpose of this rejection, the Examiner is interpreting the claim language to literally mean the number of cells actually infected with HIV in comparison to the total number of cells which are capable of being infected (see p. 2, lines 6-8 of the specification). Thus, the claimed methodology would need to measure and estimate both the number of productively and latently infected cells. It would also need to provide an accurate assessment of the total number of $CD4^+$ cells (which would include immature and mature lymphocytes from various compartments).

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

Inadequate Direction/Guidance Provided

1) The claimed invention fails to accurately measure or estimate the number of cells infected with HIV. The claimed invention simply measures the number of cells in any given sample that are expressing cell-surface gp120. However, it has been well-documented that HIV exists in a quiescent form in various lymphocyte populations (Gunthard *et al.*, 1999; Finzi *et al.*, 1999). Thus, these cells would not be expected to express cell-surface gp120, yet, the are productively infected. Accordingly, it appears that the claimed methodology would not accurately measure the true number of HIV-infected cells. Moreover, it has also been well-documented that HIV can infect various other $CD4^+$ and $CD4^-$ cell populations (e.g., B-lymphocytes, dendritic cells, $CD8^+$ lymphocytes, etc.) (Gras *et al.*, 1993; Mercure *et al.*, 1993). Thus, in order for the skilled artisan to get an accurate assessment of the true number of infected cells, these other population should also be considered. Moreover, the claimed methodology fails to perform any meaningful quantitative determinations (i.e., determining the actual number of infected cells through some procedure, determining the actual number of uninfected cells through some procedure, comparing the various populations of infected/uninfected cells to arrive at a suitable value, demonstrating how that value is useful to make any given determination or prediction) that would lead to a useful value.

2) The disclosure fails to provide adequate guidance pertaining to the sensitivity of the claimed methodology. In order for any given diagnostic assay to be useful, a number of factors need to be evaluated including the following: the assay sensitivity (or the limits of detection), the true-positive test rate, the false-negative test rate, the assay specificity (or the percentage of patients without the disease who will display a negative result), the true-negative (TN) test rate, the false-positive (FP) test rate, the predictive value (PV) (or the probability that the test

result is correctly indicating the presence or absence of the disease of the infectious agent), the efficiency, or percentage of all results that are true, and the accuracy of the recited diagnostic assay (Strongin, 1992). The disclosure is silent concerning the various factors. Furthermore, it has been well-documented that the sensitivity of the assay will vary depending upon the immunological reagents employed due to variation in antibody specificity, affinity, avidity, and other properties. Thus, the immunological reagent employed will have a dramatic effect on the assay results (Zolla-Pazner *et al.*, 1995). Other factors affecting the test results may includes the oligoclonal nature of infecting viruses, the various states of glycoprotein processing and glycosylation on the surfaces of infected cells, and the degree to which different viruses shed gp120 which may bind to the surfaces of uninfected cells. However, the disclosure is silent pertaining to any of these concerns and to the utilization of suitable immunological reagents.

Moreover, the disclosure and declaration appear to suggest that the patient has already tested negative by at least one standard virological assay. Thus, it is not readily manifest, absent further manipulation to the patients PBMCs, that a sufficient number of cells expressing cell-surface gp120 are present in the patient. The co-culture assay initially employed relies upon the expression of gp120. Since the assay was negative, the skilled artisan could reasonably assume that such patients are expressing minute quantities of antigen, if any. Accordingly, simply using an antibody-based assay, absent further sample manipulation, would not be expected to produce the desired result.

3) The disclosure fails to demonstrate that gp120/CD4$^+$ ratios are useful markers for predicting disease progression or resistance to antiviral therapy. The identification of suitable markers that correlate with patient survival or clinical efficacy of antiviral

therapy has been largely unsuccessful (Pedersen *et al.*, 1992; Molina *et al.*, 1994). This is not surprising considering the complexity of the virus and attendant immunopathology. Nothing in the disclosure adequately demonstrates that gp120/$CD4^+$ ratios are predictive of either survival or antiviral efficacy.

Absence of Working Embodiments

4) The disclosure fails to provide any bona fide working embodiments demonstrating that the claimed methodology actually accomplishes the desired task. Reference is made to an example in the specification but it fails to provide any data or details demonstrating that the claimed methodology functions in the desired manner.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

37 C.F.R. § 1.132

Applicants' arguments and the declaration filed under 37 C.F.R. § 1.132 by Jennifer Grayson are insufficient to overcome the rejection. The declaration simply states that a correlation was established between the BTI numbers and Mr. Kabat's identification numbers. However, the disclosure fails to provide any details describing the patient population (i.e., were the patients currently receiving antivirals), initial $CD4^+$ lymphocyte numbers, the precise methodology that was employed (i.e., how was the experiment conducted, what reagents were used, what cell populations were studied, positive/negative controls, etc.), the precise assay results, and appropriate conclusions pertaining to the data. Thus, the declaration is clearly insufficient and the arguments contained in the response fail to proffer any evidence that would lead the skilled artisan to conclude that the claimed invention is enabled.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

As noted above, it is not readily manifest if the claims are directed toward a method of detecting HIV or some other function. Accordingly, for the purpose of this rejection, the claims are being treated as simply directed toward a method of detecting HIV and determining the number of infected/uninfected cells.

Claims 1-3, 5-12, and 14-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over King and Hallowitz (1998) in view of Zolla-Pazner *et al.* (1995). King and Hallowitz disclose a method of detecting HIV-infected cells in a patient sample employing gp120-specific immunological reagents and magnetic particles to separate and identify gp120-expressing cells (see cols. 9 and 10). This teaching does not specifically disclose detecting the number of $CD4^+$ lymphocytes as well. However, this reference does note that the HIV-infected cells express CD4 (see Figure 1).

Zolla-Pazner *et al.* (1995) describe methods for determining the number of HIV-infected $CD4^+$ cells employing single-, double-, and triple-color staining assays involving gp120- and CD4-specific immunological reagents (see MATERIALS AND METHODS, p. 3808). Various gp120-specific antibodies were employed and the number of infected cells, based upon cell surface gp120 expression, was determined. This teaching does not disclose a methodology that employed patient samples.

However, it would it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to assess the infectivity status of an infected patient by ascertaining the number of $CD4^+$ cells, as taught by Zolla-Pazner *et al.* (1995), that express a gp120 on the cell surface, as provided by King and Hallowitz (1998), since this would provide a rapid and facile method for assessing the patient's true infectivity status. Comparing the number of $gp120^+$ cells to the number of $CD4^+$ cells would allow the skilled clinician to accurately assess the number of HIV-infected cells.

Claims 4 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over King and Hallowitz (1998) in view of Zolla-Pazner *et al.* (1995), and further in view of Bottarel *et al.* (1999).

Neither King and Hallowitz (1998) nor Zolla-Pazner *et al.* (1995) disclose detection methods employing fluorescence resonance energy transfer (FRET) assays. Bottarel *et al.* (1999) provide FRET assays that enable the skilled artisan to measure multiple cell surface antigens (e.g., gp120, CD4, CD95, etc.). This teaching does not disclose a detection assay involving assessing the infectivity status of a patient.

However, it would it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to assess the infectivity status of an infected patient by ascertaining the number of $CD4^+$ cells, as taught by Zolla-Pazner *et al.* (1995), that express a gp120 on the cell surface, as provided by King and Hallowitz (1998), employing a FRET assay, as taught by Bottarel *et al.* (1999), since this assay format provides an accurate and reliable means for detecting cell surface antigens.

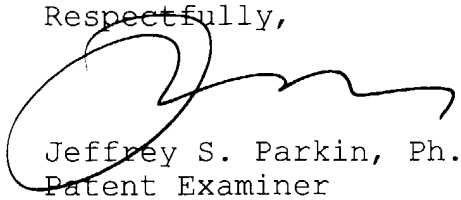
Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further

guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,



Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

13 June, 2004